

Variant: *NM_000162.5(GCK):c.1132G>A (p.Ala378Thr)*

Version: 1.0

CA126216 [↗](#)

16145 (ClinVar) [↗](#)

Gene: GCK ([HGNC:2645](#))

Condition: monogenic diabetes ([MONDO:0015967](#))

Inheritance Mode: Semidominant inheritance

UUID: 842ba46d-dc6f-44fd-8d92-daf3ce162363

Approved on: 2023/8/7

Published on: 2023/8/7

HGVS expressions

NM_000162.5(GCK):c.1132G>A (p.Ala378Thr)

NM_000162.5:c.1132G>A

NC_000007.14:g.44145618C>T

CM000669.2:g.44145618C>T

NC_000007.13:g.44185217C>T

CM000669.1:g.44185217C>T

NC_000007.12:g.44151742C>T

NG_008847.1:g.48806G>A

NG_008847.2:g.57553G>A

ENST00000395796.8:c.*1130G>A

ENST00000616242.5:c.*252G>A

ENST00000683378.1:n.358G>A

ENST00000336642.9:c.166G>A

ENST00000345378.7:c.1135G>A

ENST00000403799.8:c.1132G>A

ENST00000671824.1:c.1195G>A

ENST00000672743.1:n.144G>A

ENST00000673284.1:c.1132G>A

ENST00000336642.8:c.184G>A

ENST00000345378.6:c.1135G>A

ENST00000395796.7:c.1129G>A

ENST00000403799.7:c.1132G>A

ENST00000437084.1:c.1081G>A

ENST00000459642.1:n.512G>A

ENST00000616242.4:c.1129G>A

NM_000162.3:c.1132G>A

NM_033507.1:c.1135G>A

NM_033508.1:c.1129G>A

NM_000162.4:c.1132G>A

NM_001354800.1:c.1132G>A

NM_001354801.1:c.121G>A

NM_001354802.1:c.-9G>A

NM_001354803.1:c.166G>A

NM_033507.2:c.1135G>A

NM_033508.2:c.1129G>A

NM_033507.3:c.1135G>A

NM_033508.3:c.1129G>A

Pathogenic**Met criteria codes** 7

PP1_Strong PS4 PP2 PP3
PM5_Supporting PM2_Supporting
PP4_Moderate

Evidence Links 0**Expert Panel**[Monogenic Diabetes VCEP](#)**Criteria Specification Information**

- [Criteria Specification:](#) *ClinGen Monogenic Diabetes Expert Panel Specifications to the ACMG/AMP Variant Interpretation Guidelines for GCK Version 1.2.0*
- [Criteria Specification Approval History](#)
- [Criteria Specifications for this VCEP](#)

Evidence submitted by expert panel***Monogenic Diabetes VCEP***

The c.1132G>A variant in the glucokinase gene, GCK, causes an amino acid change of alanine to threonine at codon 378 (p.(Ala378Thr) of NM_000162.5. This variant failed quality control check in gnomAD 2.1.1; however, it is absent in multiple large population cohorts (UKBiobank, BioMe, Geisinger, internal lab contributors) and therefore the ClinGen MDEP has approved the application of PM2_Supporting for this variant (PM2_Supporting). This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.921, which is greater than the MDEP VCEP threshold of 0.70 (PP3). Another missense variant, c.1133C>T (p.(Ala378Val)), has been classified as pathogenic by the ClinGen MDEP VCEP but has a greater Grantham distance than p.Ala378Thr (PM5_Supporting). Additionally, GCK is defined by the ClinGen MDEP VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2). This variant has been identified in over 30 unrelated individuals with non-autoimmune/insulin-dependent diabetes (PS4; PMID 18248649, PMID 16965331, internal lab contributors). This variant segregates with diabetes in 15 informative meioses in a large extended family with diabetes (PP1_Strong; internal lab contributor). This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributors). In summary, c.1132G>A meets the criteria to be classified as pathogenic for monogenic diabetes. ACMG/AMP criteria applied, as specified by the ClinGen MDEP (specification version 1.2.0, approved 6/7/2023): PM2_Supporting, PP3, PM5_Supporting, PP2, PS4, PP1_Strong, PP4_moderate.

Met criteria codes

PP1_Strong		✓	This variant segregates with diabetes in 15 informative meioses in a large extended family with diabetes (PP1_Strong; internal lab contributor).
PS4		✓	This variant has been identified in over 30 unrelated individuals with non-autoimmune/insulin-dependent diabetes (PS4; PMID 18248649, PMID 16965331, internal lab contributors).
PP2		✓	GCK is defined by the ClinGen MDEP VCEP as a gene that has a low rate of benign missense variation and where pathogenic missense variants are a common mechanism of disease (PP2).
PP3		✓	This variant is predicted to be deleterious by computational evidence, with a REVEL score of 0.921, which is greater than the MDEP VCEP threshold of 0.70 (PP3).

PM5_Supporting			Another missense variant, c.1133C>T (p.(Ala378Val)), has been classified as pathogenic by the ClinGen MDEP VCEP but has a greater Grantham distance than p.Ala378Thr (PM5_Supporting).
PM2_Supporting			This variant failed quality control check in gnomAD 2.1.1, however it is absent in multiple large population cohorts (UKBiobank, BioMe, Geisinger, internal lab contributors) and therefore the ClinGen MDEP has approved the application of PM2_Supporting for this variant (PM2_Supporting).
PP4_Moderate			This variant was identified in an individual with a clinical history highly specific for GCK-hyperglycemia (FBG 5.5-8 mmol/L and HbA1c 5.6 - 7.6% and negative antibodies) (PP4_Moderate; internal lab contributors).

Curation History 		
▼ ▼		
Showing 1 to 1 of 1 rows		

The information on this website is not intended for direct diagnostic use or medical decision-making without review by a genetics professional. Individuals should not change their health behavior solely on the basis of information contained on this website. If you have questions about the information contained on this website, please see a health care professional.